

**REMARKS**

Claims 5, 9-16, 19-23, 26 and 30-64 are pending and under examination in the subject application. Claims 5, 9, 19-22, 26, 31, 32, 33, 35-39, 41, 49-52, 54, 57, 58 and 61-64 have been amended. Support for the amendment can be found throughout the application as filed. Support for the amendment directed to multiplex methods and a plurality of target sequences can be found at, for example, page 6, lines 7-22; page 13, lines 10-12; page 13, lines 18-20; page 14, lines 12-13; page 38, line 31 through page 39, line 15, and page 41, lines 1-10. Support for the amendment directed to a plurality of 96 ligation probes can be found at, for example, page 6, line 7; page 13, lines 9-12; page 14, lines 12-13; page 15, lines 9-10; page 38, line 31 through page 39, line 15, and page 41, lines 1-10. Because the claims now recite a plurality of target sequences and a plurality of ligation probes, the claims have been further amended to indicate proper antecedent basis, for example, by identifying individual members of particular pluralities using the term "each." Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the rejections set forth in the Office Action mailed April 5, 2007, and respectfully traverse all grounds for the reasons that follow.

Applicants would like to thank Examiner Lu for extending a personal interview with Applicants' representatives on May 7, 2007. In particular, Applicants' representatives discussed with Examiner Lu the unobviousness of the claimed invention. The Examiner indicated that he would favorably consider a declaration to this effect. The amendments above and supporting remarks below are believed by Applicants to substantially conform to the subject matter discussed in the interview.

**Rejections Under 35 U.S.C. § 103**

Claims 5, 13, 32, 39, 45 and 57 stand rejected under 35 U.S.C. § 103(a) as obvious over Barany et al., U.S. Patent No. 6,534,293 ("Barany et al."), in view of Schneider et al., U.S. Patent No. 4,882,269 ("Schneider et al."). The Examiner alleges that Barany et al. describe detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reactions. Schneider et al. is alleged to describe immobilizing a hybridization complex formed in solution to a solid support. The Examiner concludes that it would have been obvious to one of ordinary

skill at the time the invention was made to immobilize a ligation complex as described by Barany et al. to a solid support as described by Schneider et al. allegedly because such an immobilization would enhance separation of the complex from unhybridized probes and the signal generated from the immobilized complexes.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The Supreme Court in *KSR* stated that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR Int’l. Co. v. Teleflex, Inc., et al.*, 127 S. Ct. 1727 (2007). The Supreme Court noted that inventions in most, if not all, instances rely upon building blocks “long since uncovered.” Thus, claimed discoveries will generally be combinations of what is already known. *KSR* requires that an Examiner provide “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *Id.* at 1741. An Examiner must “identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does,” *Id.* Furthermore, the Examiner must make “explicit” this rationale of “the apparent reason to combine the known elements in the fashion claimed,” including an explanation of “the effects of demands known to the design community or present in the marketplace” and “the background knowledge possessed by a person having ordinary skill in the art.” *Id.* It is respectfully submitted that the current Office Action falls short of providing the analysis described by the Supreme Court in *KSR*.

The Examiner concedes, at page 4 of the current Action, that Barany et al. fail to teach immobilizing a ligation complex to a solid support as recited in step c) of claim 5, 32, 39 and 57, but argues that Schneider et al. cures this deficiency. The Examiner concludes that it would have been obvious to the skilled artisan to immobilize a ligation complex as described by Barany et al. to a solid support as described by Schneider et al. allegedly because such an immobilization would enhance separation from unhybridized probes and enhance the resultant signal from the

immobilized complexes. In *KSR*, the Supreme Court indicated that a reason to combine references can be based on a “need or problem known in the field of endeavor at the time of invention and addressed by the patent.” *Id.* at 1742. The references provide no hint of a need or problem that would have provided the motivation to combine the references and none is articulated in the Office Action. Applicants respectfully submit that none exists.

As amended, base claims 5, 26, 32, 33, 39, 54, 57 and 58 require, *inter alia*, identification of a nucleotide at a detection position for a plurality of target sequences using at least 96 first and second ligation probes. Base claims 5, 32, 39 and 57 additionally require immobilizing ligation complexes to a solid support. It is respectfully suggested that the amendments herein render the present rejection moot.

Barany et al. do not teach or suggest identification of plurality of target sequences using a plurality of 96 first and second ligation probe wherein ligation complexes are immobilized to a solid support.. Furthermore, there is no indication in Barany et al. that suggests that the inventors encountered difficulties in the identification of a nucleotide at a detection position that created a demand for modification of the invention to allow for easier identification. Rather, Barany et al. describe a ligation detection reaction where the products following amplification are captured on an array. Schneider et al. describe a hybridization for polymerase chain reaction (PCR) amplification. Schneider et al. contains no suggestion of performing a first immobilization step of hybridization complexes with a second immobilization step to capture amplified products because Schneider et al. detect amplified products using (see e.g., col. 21, line 42 – col. 22, line 23). Thus, while the cited references provide fragments of the claimed elements, they do not add up to the claimed invention as required under the law. Moreover, as discussed above, the Examiner has not made the *prima facie* case required.

Further, in *Graham v. John Deer Co.*, the Supreme Court held that consideration of secondary indicators of nonobvious is required. 383 U.S. 1, 17-18 (1966). *Graham* listed (1) commercial success, (2) long-felt but unsolved need and (3) failure of others as indicators to be considered. *Id.* Other secondary indicators also have been considered, including unexpected results (*Allen Archery, Inc. v. Browing Mfg. Co.*, 819 F.2d 1087, 1092 (Fed Cir. 1987); *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000).

While not conceding that the Examiner has established his burden, Applicants pointed to the unexpected results obtained using the claimed immobilization of ligation complexes. Applicants submit herewith declarations by Drs. Jian-Bing Fan and Min-Jui Richard Shen (Exhibits A and B, respectively) providing evidence and attesting that the claimed immobilization of ligation complexes was surprising and unexpected.

In Exhibit 1, Dr. Fan provides a side-by-side comparison of the claimed method employing immobilization of ligation complexes and the same method without such an immobilization. Dr. Fan attests, and the evidence shows, that the method without the immobilization step yields essentially random results. The claimed method employing immobilization of ligation complexes in a multiplex format greater than 96 produces accurate and reproducible results yielding on the average for measurements indicative of accuracy and reproducibility 98.9 and 98.2 percent, respectively.

In Exhibit 2, Dr. Shen attests that the achievements in the art at the time the invention was made for determining multiple nucleotide positions in a common mixture were significantly lower than the claimed method. Dr. Shen further attests that the results of the method of the invention were considered surprising and unprecedented, even to those skilled in the art. Dr. Shen further points out that in comparison, a ligation-based assay that does not employ the immobilization step of the claimed invention, more than seven years after the applications was filed has still been unable to achieve this goal. Despite prior advertising in as late as 2003 that a system would be marketed to multiplex at the claimed levels, the manufacture of this ligation-based assay still limits its multiplex capabilities to only 48 different determinations.

Assuming *arguendo* that the Examiner has established his burden, the above indicia of nonobviousness rebut any *prima facie* case of obviousness. Accordingly, in view of the amendments and remarks herein, Applicants respectfully request removal of the rejection of claims 5, 13, 32, 39, 45 and 57 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barany et al., U.S. Patent No. 6,534,293, in view of Schneider et al., U.S. Patent No. 4,882,269.

Applicants respectfully traverse the rejection of claims 14-16, 34, 46-48 and 60 under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al., in view of Schneider et al. and further in view of Walt et al., U.S. Patent No. 6,327,410. For the reasons set forth above with respect to

the base claims from which these depend from, it is respectfully submitted that the Examiner has not met the *prima facie* burden of articulating a reason to combine the cited references. Moreover, assuming *arguendo* that the Examiner has established his burden, the above indicia of nonobviousness in the form of declarations and evidence by Drs. Fan and Shen rebut any *prima facie* case of obviousness.

Applicants similarly traverse the rejection of claims 26, 33, 54, 58 and dependent claims 10, 13, 19-22, 31, 35, 42, 49-52, 56, 59 and 61 under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al., U.S. Patent No. 6,027,889 (1997) in view of Zhang et al., U.S. Patent No. 5,876,924. For the reasons stated of record and set forth above with respect to the identification of nucleotide positions in a plurality of target sequences using at least 96 first and second ligation probes, it is respectfully submitted that the Examiner has not met the *prima facie* burden of articulating a reason to combine the cited references. Moreover, assuming *arguendo* that the Examiner has established his burden, the declarations by Drs. Fan and Shen as indicia of nonobviousness rebut any *prima facie* case of obviousness.

Similarly, with respect to claims 11, 12, 43 and 44, standing rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al. as applied above and further in view of Gebeyehu et al., U.S. Patent No. 4,921,805; claims 9, 23, 30, 41, 53, and 55, standing rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., as applied above, and further in view of Seradyn Particle Technology; Claims 37 and 63, standing rejected under 35 U.S.C. § 103(a) as allegedly obvious over Barany et al. in view of Zhang et al., and further in view of Monforte et al., U.S. Patent No. 5,830,655; claims 36 and 62, standing rejected under 35 U.S.C. § 103(a) over the above combination of references and further in view of Brown et al., U.S. Patent No. 5,807,522, and claims 38 and 64 standing rejected under 35 U.S.C. § 103(a) over the combination of Barany et al. in view of Zhang et al. and Monforte et al. and further in view of Johnson et al., Applicants similarly contend for the reasons above and previously of record, it is respectfully submitted that the Examiner has not met the *prima facie* burden of articulating a reason to combine the cited references. The submitted declarations by Drs. Fan and Shen as indicia of nonobviousness rebut any alleged *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of all grounds of rejection.

**CONCLUSION**

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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